REMARKS

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims (with appropriate defined status identifiers) is presented above. Upon entry of the amendments, claims 1, 7-9, 12-16, 19, 21, 23, 33, 35-37, 48-49, 52, 54-55 and 58-62 will be pending. Applicant respectfully requests reconsideration of those claims in view of the foregoing amendments and the remarks set forth below.

Applicant thanks the Examiner for issuing a non-final Office Action to take into consideration the supplemental response filed June 19, 2003, which had not been considered when the September 9, 2003 Office Action was issued. Applicant believes that the foregoing amendments and following remarks address the remaining issues and place the application in condition for allowance.

Claim Amendments

Claims 1 and 24 are amended to recite that the pharmaceutical composition is administered via localized delivery and that the pharmaceutical composition comprises a herpes simplex virus vector comprising an expressible nucleotide sequence for a soluble co-stimulatory factor in the B7 family. Claims 33 and 35 and 48 and 49 are amended to depend from claim 23, and claims 48 and 49 are further amended to clarify that the vector is a herpes simplex virus vector. Claims 58-62 are added to recite specific embodiments of the invention where the soluble co-stimulatory factor is B7-1-Ig, B7-2 or B7-2-Ig. These amendments do not introduce new matter into the application.

Claim 2 is canceled as being redundant in view of amended claim 1. Claims 24-30, 53 and 57 are canceled as being redundant in view of claim 1 and claims dependent therefrom. Claims 32 and 56 are canceled as being redundant in view of claim 23 and claims dependent therefrom.

Indefiniteness Rejection

Claim 57 was rejected as being indefinite for lacking antecedent basis. The cancellation of this claim obviates the rejection.

Pending Enablement Rejections

As set forth at page 3 of the Action, the Examiner raises three separate questions regarding the enablement of the claimed invention: (1) whether the specification enables soluble co-stimulatory molecules other than B7-1-Ig or B7-2-Ig; (2) whether the specification enables vectors other than HSV vectors, and (3) whether the specification enables vectors that must target particular types of cells. For the reasons already of record, Applicant disagrees with the Examiner's position on the need for HSV vectors and for local delivery. To expedite prosecution, however, Applicant has amended the claims to obviate these concerns. Thus, the instant claims recite HSV vectors and local delivery. Applicant addresses below the Examiner's other concern, the enablement of soluble co-stimulatory factors in the B7 family.

At page 6, the Office Action asserts that the evidence of record, including the specification and publications by Kato, Kanner, Noelle and Hurtado, demonstrates that "it was within the skill of the artisan to make a soluble co-stimulatory molecule comprising the extracellular domain of a co-stimulatory molecule and IgG, [but] does not provide enablement for making soluble co-stimulatory molecules that do not contain IgG." As explained below, however, IgG is not a required component of the soluble co-stimulatory factors of the B7 family useful in the present invention.

The specification objectively enables soluble co-stimulatory factors of the B7 family at, for example, page 3, lines 19-21, where it teaches that soluble co-stimulatory factors "of the B7 family" are preferred for use in the invention. Additional support is found at page 7, where the specification teaches that the invention is "not limited to B7-1," and lists other co-stimulatory factors that can be used. The teachings regarding co-stimulatory factors comprising IgG describe IgG-linked dimers as a preferred embodiment. Those skilled in the art reading the specification would understand that IgG is not a required component of the soluble co-stimulatory factors of the invention, but only an optional aspect of the invention.

Given the specification's objective enablement of the claimed soluble co-stimulatory factors, the Examiner cannot make out a proper rejection for lack of enablement without providing "evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Cortright,* 165 F.3d 1363 (Fed. Cir. 1999). Instead of citing such evidence, however, the present rejection merely cites an absence of teachings in the prior art of record of the claimed factors lacking IgG. That such soluble co-stimulatory factors are not described in the literature of record does not suggest that those

skilled in the art would not have been able to make and use them in accordance with the claimed invention, based on the guidance set forth in the specification. With this response, moreover, Applicant submits further evidence that this aspect of the claimed invention is enabled, as explained below.

The ability of those skilled in the art to make soluble co-stimulatory factors of the B7 family without undue experimentation is supported by Fields *et al.*, *J. Immunol.* 161: 5268-75 (1998) (copy attached). Fields relied on the well-known principles of protein targeting mechanisms to construct a soluble B7 protein. Generally, the presence of an N-terminal or internal signal sequence leads to the transport of the nascent amino acid chain to the membrane of the endoplasmatic reticulum, and the presence of a transmembrane domain determines whether the protein stays in the membrane or is transported into the lumen of the endoplasmatic reticulum and finally becomes secreted into the extracellular space. Thus, Fields created a soluble B7 protein simply by deleting the transmembrane domain together with the cytoplasmamtic domain. Fields manipulated the protein further, by constructing dimers using an Ig spacer, but that manipulation did not contribute to the solubility of the protein. Accordingly, Fields demonstrates that those skilled in the art, guided by the teachings of the specification and armed with the general knowledge of protein targeting mechanisms, readily would have been able to make soluble co-stimulatory factors of the B7 family, without providing an Ig component.

Evidence that those skilled in the art would have been able to use soluble co-stimulatory factors of the B7 family without undue experimentation is provided, for example, by Kwon *et al.*, *Proc. Nat'l Acad. Sci. USA* 96: 15074-79 (1999) (copy attached). This publication teaches that the blockade of CTLA-4 can contribute to cancer therapy. (For example, see the last sentence of the abstract.) Because members of the B7 family can bind to CTLA-4, those skilled in the art would expect a soluble co-stimulatory factor of the B7 family administered in accordance with the present invention to block CTLA-4 and be useful for tumor therapy, regardless of whether the soluble co-stimulatory factor includes an Ig component. In this regard, Applicant notes that the statement in Todo *et al.*, *Cancer Res.* 61: 153-61 (2001) (copy attached), with regard to the inability of "B7-1 alone" to inhibit tumor growth referred to experiments done with *native* B7-1, and does not reflect on the activity of *soluble* co-stimulatory factors of the B7 family, as presently claimed.

With respect to embodiments where the soluble co-stimulatory factor comprises a dimer, those skilled in the art would understand from the specification, illuminated by knowledge of the relevant art,

that the dimers need not comprise an Ig linker. As the specification states at page 7, "any protein or peptide sequence that will allow [the molecules] to cross-link their cognate receptors can be used" as a linker to form dimers. Fields describes the construction of soluble B7-Ig fusion proteins where the hinge CH2-CH3 domains were used as a flexible spacer, but other flexible spacers are known, and those skilled in art would have understood that any such spacers can be used to join the dimers.

In validation of the enabling quality of the present specification, vis-à-vis B7 family members other than B7-1 and B7-2, Applicant also would have the Examiner note certain information about the family. There are a number of factors, related to B7-1, that play a role in T-cell activation, and additional such factors are being identified as the field develops. Members of the B7 family share a distinctive domain organization, reviewed by Henry *et al.*, *Immunol. Today* 20: 285-88 (1999) (copy attached). As Figure 1 of the Henry article shows, family members comprise an extracellular IgV domain, an optional extracellular IgC domain, a transmembrane domain and more variable intracellular domains.

In light of this information about the B7 family, those skilled in the art would have appreciated that Applicant's express teachings regarding B7-1 and B7-2 are readily applied to other family members, as indicated at page 3 of the specification. Those skilled in the art would have been able to make soluble versions of such other family members by, for example, following procedures similar to those of Fields and deleting at least the transmembrane domain of the protein.

The foregoing demonstrates that the specification fully enables those skilled in the art to practice the claimed invention with respect to soluble co-stimulatory factors of the B7 family. Accordingly, the Examiner is respectfully urged to reconsider and withdraw the remaining enablement rejection.

Applicant believes that the application is now in condition for allowance, and an early notice to that effect is respectfully requested. The Examiner is invited to contact the undersigned, to address any issues that may remain.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 CFR §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are

needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 CFR §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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